

Assessing liver tumor stiffness by transient elastography

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Abstract

Background and aims Transient elastography is a novel noninvasive method to assess liver fibrosis by measuring liver stiffness. This study is a first step toward the provision of a noninvasive measurement of hepatic tumor stiffness by transient elastography.

Patients and methods Patients with liver tumor larger than 5 cm in diameter and located near the liver surface were enrolled between June 2004 and February 2005. Histology of each tumor was evaluated on ultrasound-guided liver biopsy specimens. Transient elastography (Fibroscan, Echosens, Paris) was used to measure tumor stiffness. Tumor stiffness was measured as follows. First, by using B-mode ultrasound, we searched for the optimal right intercostal position for tumor stiffness measurement while keeping the ultrasound probe and body surface at right angles. Then the vibrator for transient elastography was applied at the same position and angle, and stiffness was measured according to the manufacturer's instruction.

Results Tumor stiffness was measured in 40 patients, 17 with hepatocellular carcinoma (HCC), six with cholangiocellular carcinoma (CCC), 16 with metastatic tumors (mostly adenocarcinoma), and one with malignant lymphoma. The median value was 55 kPa in HCC, 75 kPa in CCC, 66.5 kPa in metastatic tumor, and 16.9 kPa in

malignant lymphoma. The stiffness value of CCC was significantly higher than that of HCC and metastatic tumors ($P = .049$).

Conclusion We showed that stiffness of liver tumors could be measured with transient elastography. Improvements in the device, such as smaller and variable region of interest of measurement and real-time B-mode display, may ensure wider clinical application.

Keywords Ultrasonography · Liver neoplasms · Stiffness · Elastography

Abbreviations

CCC	Cholangiocellular carcinoma
CT	Computed tomography
HCC	Hepatocellular carcinoma
RFA	Radiofrequency ablation
ROI	Region of interest
TACE	Transcatheter arterial chemoembolization

Introduction

Tissue stiffness is related to tissue composition, which is often changed by disease. For millennia, physicians have used palpation as a part of the physical examination to detect pathology. The ubiquitous presence of stiffer tissue associated with pathology often represents an early warning sign for disease, as in the cases of breast or prostate cancer. This implies that methods for estimating stiffness of tissues would add a weapon to the medical armamentarium. It is therefore of interest to measure the stiffness in an objective and noninvasive way, and techniques to estimate the mechanical response of deep tissues to external excitations have been proposed [1–7].

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The increased use of radiologic imaging, particularly ultrasound examination, has led to much more frequent identification of nodules in the liver. Hepatocellular carcinoma (HCC) is increasingly associated worldwide with estimates of hepatitis B and hepatitis C prevalence [8–10]. Intrahepatic cholangiocarcinoma is firm to hard glandular tumor arising from intrahepatic bile ducts. And the liver is the most frequent site of bloodborne metastases, irrespective of whether the primary is drained by systemic or portal veins. It is involved in about a third of all cancers, including half of those of the stomach, breast, and lung and those arising from the colon.

Transient elastography (Fibroscan, Echosens, Paris, France) is a novel rapid, noninvasive, reproducible method for measuring liver stiffness [11–14]. Briefly, an ultrasound transducer probe is mounted on the axis of a vibrator; vibrations of mild amplitude and low frequency are transmitted by the transducer, inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisitions are used to follow the propagations of the shear wave and to measure its velocity. Tissue stiffness is directly proportional to the square of shear wave velocity: the stiffer the tissue, the faster the shear wave propagates. Recently, several groups reported that transient elastography accurately estimates histologically assessed fibrosis stages of the liver in patients with chronic hepatitis C. Theoretically, the elastography can also assess stiffness of hepatic tumors. However, the diameter of the tumor must be comparable to the region of interest (ROI) of transient elastography, which is currently between 25 and 65 mm from the surface. This study is a first step toward the provision of a noninvasive measurement of hepatic tumor stiffness by transient elastography.

Patients and methods

Patients

Patients with liver tumor more than 5 cm in diameter and located near the liver surface were enrolled between June 2004 and February 2005. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our institutional review board. Written informed consent was given by each patient.

Diagnosis of liver tumor

Histology of each tumor was evaluated on ultrasound-guided liver biopsy specimens obtained for diagnostic and/or therapeutic purposes. In some cases of metastatic tumors, histologic diagnosis had been made on the primary lesion. In cases of HCC, diagnoses were made by dynamic

computed tomography (CT), where intrahepatic nodules with hyperattenuation in the arterial phase and with washout in the late phase were considered as definite HCC [15].

Transient elastography principle

Fibroscan (EchoSens, Paris, France) is a medical device specifically designed for hepatic transient elastography. An ultrasonic transducer is mounted on the axis of a vibrator that induces an elastic shear wave into the liver and its propagation velocity is measured by pulse-echo ultrasound acquisitions. The measurement depth, or ROI, is set between 25 and 65 mm from the surface.

Tumor stiffness was measured as follows. First, by using B-mode ultrasound, we searched for the optimal right intercostal position where the tumor could be viewed as large in diameter and as near to the surface as possible while keeping the ultrasound probe and body surface at right angles. Then at the same position and angle, the vibrator was applied and stiffness was measured according to the manufacturer's instruction. The median value of 10 valid measurements, expressed in kilopascals, was considered representative of the elastic modulus. The measurement took about 10 min for each case.

Results

Preliminary experiments revealed several necessary conditions for tumor stiffness measurement. The target tumor should be in the right lobe of the liver because measurement from right intercostal spaces is strictly recommended in the manufacturer's instruction. Stiffness cannot be measured in the presence of ascites since shear wave does not propagate in liquid. On B-mode ultrasound scout, the nearest point of tumor should be within 20 mm from the liver surface and the span of tumor should be longer than 50 mm, so that the tumor occupies the whole ROI of stiffness measurement. Tumor stiffness could be thus measured in 40 patients, 17 with HCC, six with cholangiocellular carcinoma (CCC), 16 with metastatic tumors (mostly adenocarcinoma), and one with malignant lymphoma.

The tumor characteristics and the stiffness obtained by transient elastography were summarized in Table 1 and Fig. 1. The median value of stiffness was 55 kPa in HCC, 75 kPa in CCC, and 66.5 kPa in metastatic tumors, where the difference was statistically significant ($P = .049$ by Kruskal–Wallis test). Since the majority (five of six) of CCC cases showed stiffness exceeding the upper limit of measurement (75 kPa), the absolute difference of stiffness between HCC, metastatic tumors, and CCC may have been

Table 1 Liver tumor stiffness^a

Variables	n	Value (kPa, median)
CCC	6	73.9 (69–75)
HCC	17	55 (20.4–75)
Malignant lymphoma	1	16.9
Metastatic tumor	16	66.5 (23.6–75)
Submandibular gland	2	75 (75–75)
Esophagus	1	69.1
Stomach	2	67.8 (63.9–72)
Rhabdomyosarcoma	1	57.1
Gall bladder	3	52.5 (25.7–75)
Breast	1	48
Colon	5	46.3 (23.6–75)
Ovary	1	22.3

^a Expressed as median (minimum–maximum value).

much greater. Metastatic tumors showed intermediate stiffness (66.5 kPa); nevertheless, stiffness varied widely between each tumor.

Discussion

The modulus of elasticity, or stiffness as measured by transient elastography, is the relationship between the tensions needed to achieve a relative change of length. Thus, healthy soft tissue has higher coefficients of extension than does hard or tumorous tissue. As shown in this study, primary or metastatic liver tumors are stiffer than normal liver parenchyma (2.5–5 kPa). Moreover, stiffness thus measured varies widely according to tumor pathology. The current study showed that CCC is actually stiffer, as measured by elastography, than HCC, as is well-known to surgeons by hand. The stroma of CCC differs from that of HCC, the former consisting of fibrous tissue with little or no capillary formation.

The current study was the first attempt to assess liver tumor stiffness by using a commercially available device. Since the device is specifically designed to measure liver stiffness, there are limitations on tumor stiffness measurements. In particular, stiffness can be measured only in massive liver tumors occupying a large portion of the right lobe. This is primarily because the ROI of stiffness measurement is large and fixed, which the target tumor should cover. Technically, the ROI can be made smaller and variable, which will enable us to measure smaller tumors located deeper from the liver surface.

With future improvements, tumor stiffness measurements may have broader clinical applications. First, stiffness may differ between small HCC and noncancerous nodules although we do not currently have data on stiffness

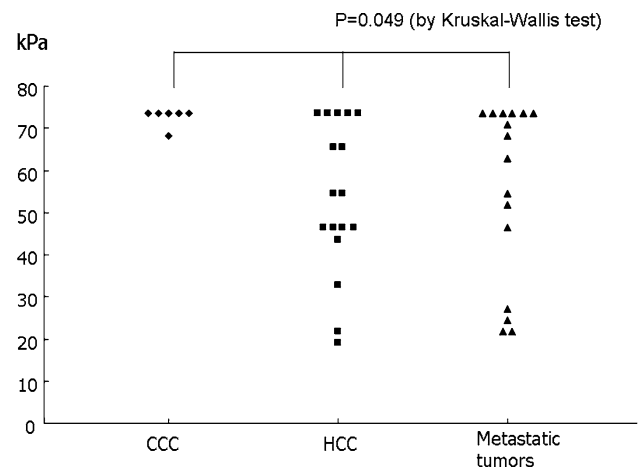


Fig. 1 Distribution of tumor stiffness values in kilopascals. Tumor stiffness is significantly higher in the CCC than HCC and metastatic tumors

of small HCC nodules. Borderline lesions are now followed up by changes in size and vascularity on contrast-enhanced CT. Liver stiffness may provide supplemental information. Second, changes in stiffness may indicate necrosis of tumor induced by radiofrequency ablation (RFA) or transcatheter arterial chemoembolization (TACE). Indeed, Varghese et al. reported in an experiment using porcine liver that necrotic liver tissue became stiffer after RFA [16, 17]. Since RFA is usually applied on small HCC, we cannot confirm this phenomenon on human HCC at present. However, improved elastography with smaller ROI of measurement may provide valuable information on efficacy of tumor ablation. TACE induces tumor necrosis by hepatic arterial ischemia. We had preliminary data that HCC became stiffer after successful TACE (data not shown).

In conclusion, we showed that stiffness of liver tumors could be measured with transient elastography. Improvements in the device, such as smaller and variable ROI of measurement and real-time B-mode display, may allow wider clinical application.

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